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Active Hyperæmia.

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(Communicated by Prof. W. M. Bayliss, F.R.S. Received January 20, 1922.)

(From the Institute of Physiology, University College, London.)

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1. Introduction.

So conflicting are the statements made by physiologists and pathologists alike, relating to the mechanism by which "an increased afflux of blood to a part" is brought about, that it was felt desirable to investigate this important phenomenon. Let us first consider the present state of knowledge regarding the possible factors involved.

(i) *Vaso-constrictor Nerves* (neuro-paralytic hyperæmia).—The existence of vaso-constrictor nerves was first demonstrated in the cervical sympathetic by Claude Bernard (1852), and independently by Brown-Séquard. The interruption of the normal stream of impulses from the vaso-motor centres along these nerves gives rise to a "neuro-paralytic hyperæmia," such as is met with surgically in wounds of the neck, or in lesions of the spinal cord. During the normal functional activity of a particular organ, reflex excitation of the vaso-constrictor nerves of the resting organs liberates a maximum blood supply for the working organ; this is a regulating mechanism of the central nervous system which ensures a more efficient functional hyperæmia of the working organ (Lovén, 1866; Bayliss, 1920).

(ii) *Vaso-dilator Nerves* (neuro-tonic hyperæmia).—The first evidence for the existence of vaso-dilator nerves was supplied by Claude Bernard (1858), who found that stimulation of the chorda tympani caused not only secretion by the submaxillary gland, but also dilatation of its blood vessels. Vulpian showed the reddening of the tongue upon stimulation of the lingual nerve, and proved that the fibres concerned came from the chorda tympani. Goltz had noticed that whereas stimulation of the sciatic nerve, when freshly cut, caused pallor of the skin of the toes and a lowering of temperature as measured by a thermometer placed between the toes, the same stimulation of the nerve two days after section caused reddening and a rise of temperature. He concluded that vaso-dilator, as well as vaso-constrictor nerves, existed in the sciatic, and that they resisted degeneration for a longer time than the vaso-constrictors. Bernstein showed that the vaso-dilator fibres in the sciatic could be excited independently by means of slow rhythmic shocks, especially in a leg which had been previously cooled.

The remarkable nature of the vaso-dilator supply to the limbs, skin of the trunk, and probably of the ears and face, and to the intestine, was not explained until 1901, when Bayliss investigated vaso-dilation in these regions produced by stimulation of the peripheral cut ends of the corresponding dorsal roots. The work of Head and Campbell (1900), on herpes zoster, shows this disease to be due to irritative lesions of the dorsal root ganglia, which give rise to abnormal impulses in an efferent (anti-dromic) direction along the sensory fibres to the skin; whether stimulation of vaso-dilator nerves can produce blisters has not yet been proved. Ninian Bruce (1910) showed that the "neurotonic hyperæmia" (Adami), produced in the conjunctiva by an irritant like oil of mustard, could be prevented by first paralysing the sensory nerves with cocaine, or by section and degeneration; this was explained as an "axon reflex," since the hyperæmia depends on the integrity of the sensory fibre.

(iii) *Vaso-dilator Substances* (a local hyperæmia).—It is generally held that the hyperæmia of inflammation arises from the action of physical and chemical agents directly upon the blood-vessel wall. The great similarity between a wheal produced by the lash of a whip, for example, and the effects of a local introduction of histamine (β-iminazolyl-ethylamine) into a lightly scarified area of skin lends support to this view, since the depressant action of histamine locally upon the capillary wall is definitely known (Dale and Richards).

What are the possible chemical vaso-dilator substances which may exert a "depressor" effect on the plain muscle or endothelium of the blood vessels of an organ so as to ensure a greater blood supply during activity? Two possibilities are presented:—

α. *Acid Metabolites*: The more or less completely oxidised products, *e.g.*, CO_2 and lactic acid, derived from the energy-producing food-stuffs.

β. *Basic* split products resulting from the wear and tear of the cell protoplasm.

(iv) *Functional hyperæmia.*—With this brief survey of the factors which produce vaso-dilation, we may embark upon the controversial question of the means whereby the functional hyperæmia of an active organ is brought about. Leaving out of the discussion the alterations in general blood pressure (*vide* (i)), the issue lies between neuro-muscular vaso-dilation and the automatic vaso-dilation produced by metabolites. On the one hand, among our best authorities we have some who regard functional vaso-dilation as a simple local effect of the metabolites resulting from activity, just as the heat evolved results from the chemical changes of activity, and there is, according to them, as little need to presume the existence of special vaso-dilator nerves as there is to suppose the presence of caloric nerves.

Barcroft (1914, p. 145) found that during stimulation of the sympathetic fibres in the submaxillary gland (cat) by means of adrenalin, the vaso-constriction ordinarily produced by adrenalin on blood vessels is more than counterbalanced by the action of the vaso-dilator substances produced when the gland secretes.

On the other hand it is well known that stimulation of the chorda tympani in an atropised submaxillary gland causes a vaso-dilation in the total absence of secretion; Barcroft explains this by advancing the possibility of lower grades of cellular activity, without external secretion occurring in such cases, and he actually found that during stimulation there was an increased oxygen intake in the atropised gland. An examination of his figures (p. 147) shows, for example, equal metabolic rates for a 4- and 2-fold blood flow:—

Per cent. increase in oxygen	55	55
Per cent. increase in blood flow	333	102

Here there must be, as Bayliss (1920) points out, a factor in addition to metabolites called into play; the hyperæmia in the last experiment can hardly be caused by metabolites arising from activity of such "subliminal degree"; it would appear that the neuro-muscular mechanism is also excited to activity. Anrep (1916) has shown that when secretin used to stimulate the pancreas is free from the depressor substance, there is little or no sign of vaso-dilation in the gland associated with secretin; this is also seen in some of the experiments of Barcroft and Starling (1904) on the gas exchanges in the pancreas. Thus, during the normal rate of activity in glandular organs, the metabolites are quickly removed and never reach a high concentration. This is not the case with skeletal muscle where a prolonged contraction compresses the blood vessels and banks up the metabolites. Asher (1910), by means of minute doses of sodium fluoride, was able to paralyse the secretory activity of glands without eliminating the vaso-dilator response, from which he concluded that vaso-dilation could occur independently of metabolites.

The present investigation is an attempt to clear up these fundamental problems:—

a. To obtain evidence, if possible, for the undoubted existence of vaso-dilator nerves.

b. To determine the relative part played by metabolites and vaso-dilator nerves in functional hyperæmia.

c. If vaso-dilator nerves actually exist and are not an essential to functional hyperæmia, what, then, is their function?

2. METHODS.

i. Measurement of vaso-dilation: *a. direct* blood flow;
b. indirect plethysmograph.
ii. Estimation of metabolites: *a. alkali reserve;*
b. lactic acid.

The preparation: The tongue, as pointed out by Anrep, possesses unique advantages for the examination of these problems: the individuality of function of its several nerves, which run separate courses, constituting an easy and very certain means of determining the cause of hyperæmia. The functional activity is almost purely muscular, since the total mass of lingual glands is of comparatively insignificant amount. Dogs were found to be the most convenient animals for these experiments which involved a good deal of operative procedure, the accessibility of the structures in these animals reducing injury to the tissues to a minimum. A preliminary dose of morphia was given and complete anæsthesia maintained by means of chloroform and ether; in the few cases in which curare was injected decerebration preceded. The lingual and hypoglossal nerves were exposed on both sides, and the blood pressure was recorded in the femoral artery.

Venous outflow: A cannula was placed in the anterior transverse vein connecting the two lingual veins, with ligatures and artery forceps so placed as to allow of the collection of samples of blood from the lingual vein while permitting the normal flow in the interval. No anti-coagulant was used, but all tubes and cannulæ were paraffined. The rate of flow was noted by a drop recorder.

For the estimation of lactic acid, 20 c.c. of blood was collected directly into 0·5 per cent. KH_2PO_4; for the determination of the P_H and alkali reserve, the blood was collected under paraffin, oxalate being used as an anti-coagulant. By attaching the hyoid bone to an isometric muscle-lever, the tongue muscles could be made to work against a resistance and develop a measurable tension (*e.g.*, fig. 5).

Plethysmograph of the tongue: The changes in volume of a curarised tongue were originally studied by Anrep (senior) and Cybulski (1884), and later with the same methods by Piotrowski (1893). For the purposes of the present investigation curarisation could not be adopted for maintaining the tongue, or rather part of it, placidly in the plethysmograph. In order to permit the normal production of metabolites, a technique had to be devised which enabled one to take reliable records of an active muscular organ. Many failures were encountered before the following arrangement was arrived at of accommodating the whole tongue in the plethysmograph and preventing its moving in and out during contraction.

The genio-hyoid muscles were detached from the symphysis of the jaw and the mucous membrane of the floor of the mouth was cut through in close contact with the alveolar margin as far back as the anterior pillars of the fauces. The tongue was now drawn out ventralwards, all bleeding arrested by ligature and cautery, and the cut edges of the mucous membrane sewn together round the genio-hyoid muscles, carefully avoiding pressure on the lingual vessels and nerves; the whole tongue could thus be placed in the plethysmograph. To prevent traction on the root of the tongue from without, a tracheal canula was inserted, the trachea being completely cut across; all muscles coming up to the hyoid were cut between ligatures, and all branches of XII, other than those to the tongue, were severed; finally, to completely immobilise the larynx and hyoid, a steel rod placed through the mouth into the larynx, and emerging from the upper end of the transected trachea, was firmly clamped to the same stand as the plethysmograph.

A plethysmograph of circular cross-section was selected which just fitted the tongue; it was fitted with a cuff of membrane rendered air-tight, yet soft, by means of vaseline. When adjusted it was covered with cotton-wool and connected to a piston recorder: time was allowed for temperature adjustment.

3. THE VASO-CONSTRICTOR NERVES.

The vaso-constrictor fibres are supposed to be derived from the cervical sympathetic and run in the hypoglossal nerves: the sympathetic fibres for the *muscles* of the tongue seem to run, not in the hypoglossal, but in the chorda tympani (Boeke, 1921).

The right vago-sympathetic trunk was ligatured in the neck, cut below the ligature, and the vagal portion was transected at its emergence from the skull. Faradisation of the peripheral end of the R. sympathetic affected the venous outflow in the manner shown in fig. 1.

During stimulation the drops are seen to become less frequent and on removal of the stimulus the still further decrease indicates that either the vessels immediately relax and accommodate the first outflow of blood, or there is a marked "after effect" following the stimulus.

Faradisation of the hypoglossal nerve in the curarised animal verifies the fact that the vaso-constrictors run in this nerve (fig. 2), as was first clearly shown by Anrep (senior).

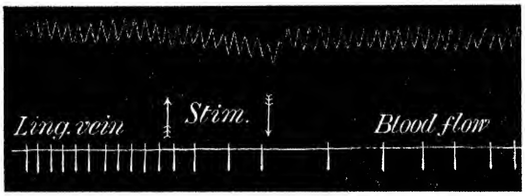

FIG. 1.

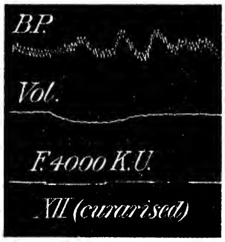

FIG. 2.

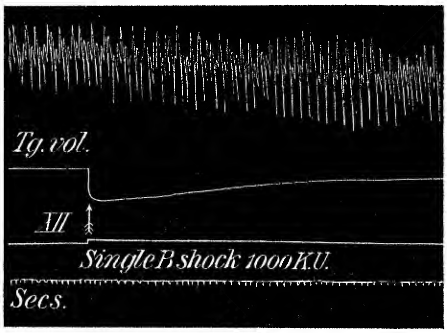

FIG. 3.

Stimulation of the made-up hypoglossal nerve with only a single shock (to avoid any appreciable "metabolite" effect) causes an emptying of the collapsible veins and capillaries by simple compression of the contracting skeletal muscle. It is here suggested that the arterioles, by the simultaneous stimulation of the vaso-constrictor nerves have their lumina rendered less liable to extinction: this would prevent a reversal of the blood stream and maintain a patent system for the onrush of blood following repeated contractions (fig. 4), or a prolonged contraction (fig. 5). It is difficult to imagine what function vaso-constrictors, bound up with a motor nerve, might serve. Fig. 5 shows the steady diminution of the tension developed in the tongue arising from the anæmia produced by its own contraction.

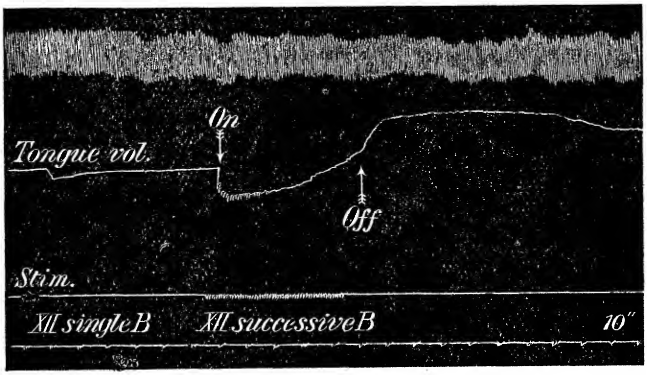

Fig. 4.

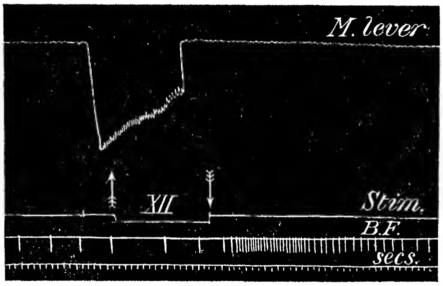

Fig. 5.

4. The Vaso-dilator Nerves.

Fig. 6, in the opinion of the writer, constitutes the most convincing single piece of evidence in favour of the undoubted existence of vaso-dilator nerves. Such a huge vaso-dilation in the absence of any muscular activity must be independent of metabolites. The effect produced by a similar shock upon the motor nerve is seen in fig. 3, where one would expect a greater production of metabolites, yet vaso-dilation is absent.

How very effective a mechanical stimulus is in evoking vaso-dilation (Bayliss, 1920), by excitation of the lingual nerve, is seen in the plethysmographic record of the tongue in fig. 7.

It must be acknowledged, however, that the vaso-dilator fibres have a long latent period (5 seconds), time enough to allow of the production of metabolites. To see the drops of venous blood issuing from the lingual vein suddenly burst into a continuous stream of bright arterial colour on stimulation of the lingual nerve while the tongue remains in a state of restful indifference, is a most simple and convincing demonstration of the individual existence of vaso-dilator nerves.

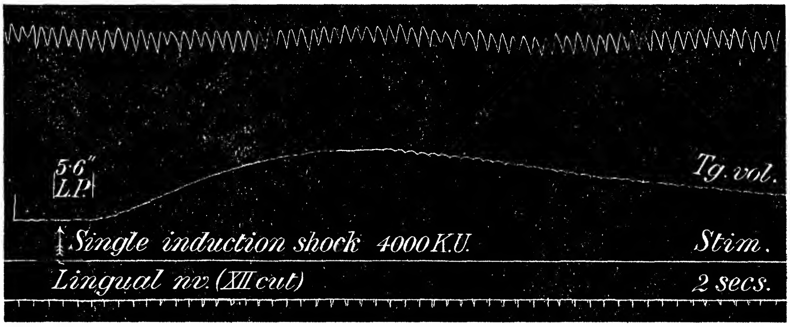

Fig. 6.

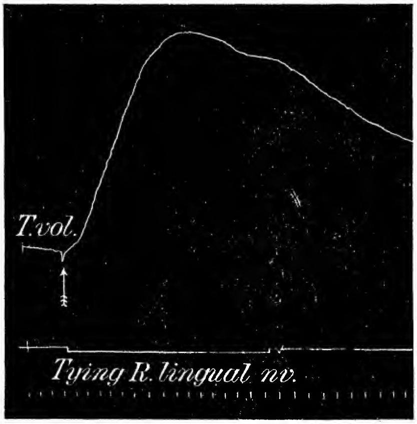

Fig. 7.

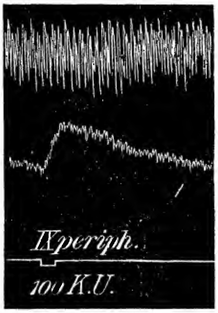

Fig. 8.

Let us examine further the theory which explains vaso-dilation by the action of metabolites. This theory has been based upon the metabolism of the submaxillary gland as measured by its oxygen intake, which is found to be increased in all conditions in which vaso-dilation accompanies excitation of its nerves, and this increased gaseous metabolism only slowly dies down (Barcroft and Kato, 1915). The oxygen consumption in the tongue has been recently measured by Anrep and Evans (1920), and the mean result of their experiments is shown in the following Table.

	Flow of blood.	Oxygen used.
	c.c./min.	c.c./min.
During rest	0·59	0·144
Stimulation of lingual nerve	2·85	0·142

From this it will be seen that the stationary oxygen consumption lends no support to the metabolite theory for the explanation of the five-fold increase of blood flow obtained by these experimenters.

Measurement of the alkali reserve of the blood from the lingual vein and the blood from the femoral artery during stimulation of the lingual nerve shows them to be practically identical. This is seen in the following figures, obtained from different dogs under widely varying conditions:—

Stimulation of lingual nerve.	Alkali reserve of plasma.					
Lingual vein	49·5	53·5	67·0	69	70	48·5
Femoral artery	49·5	54·0	67·5	69	70	49·0

Thus, interrupted faradisation of the lingual nerve produces no measurable difference in the alkali reserve (CO_2 metabolite), even when the vaso-dilation is so great as to increase the blood-flow five to eight times, as in the above experiments (of course, the dilution of the metabolite proceeds at the same rate). In so far as gaseous metabolites are concerned, there is no denying the existence of vaso-dilator nerves.

Furthermore, no real difference was detected in the lactic acid-content of the blood issuing from the tongue during stimulation of the lingual nerve as compared with that in the arterial femoral blood, *e.g.*, femoral artery, 6·4 mgrm. per 100 c.c.; lingual vein, 6·0 mgrm. per 100 c.c.

If vaso-dilator substances are produced when the lingual nerve is excited, then they must necessarily be of a non-oxidative character and presumably of a very powerful nature; the later stages of this investigation will show that such an assumption is unnecessary, since the vaso-dilator nerves of the tongue possess independent functions, and are not subservient to the functional activity of the tongue muscles.

The glossopharyngeal, the sensory nerve of the posterior third of the tongue, responds to stimulation just as the lingual does, but in a milder degree (fig. 8); either it contains specific vaso-dilator fibres (*via* tympanic branch, Loeb and Eckhard), or it is capable of conducting anti-dromic vaso-dilator impulses similar to those found by Bayliss (1901) in the sensory nerves of the limbs.

5. Metabolites.

Gaskell (1880) was the first to lay stress on the importance of the local vaso-dilator action of acid metabolites; he observed the effect of lactic acid on the curarised mylo-hyoid of the frog, and measured with a micrometer eye-piece the dilatation of the blood-vessels. About the same time Severini put forward the view that " the increased flow of blood through an organ when it is in a condition of activity is due to the trophic dilatation of the capillaries, and not to relaxation of the vascular muscle." He stated that oxygen diminishes the size of the capillary lumen, because the nucleus of the cells of the capillary wall (nucleus of Golubew) becomes more spherical, while conversely with the action of CO_2 it flattens out in the cell, and so the lumen is greater.

More recently, Krogh (1919) has observed the circulation in the thin muscles of frogs and guinea-pigs, chiefly by reflected light, with a binocular microscope; he finds that when muscles contract, either spontaneously or as a result of artificial stimulation, many more capillaries spring into view, and when the contraction is over they disappear again; capillary dilatation also occurs when certain irritants and narcotics are applied locally to the tissue, and in these cases the capillary dilatation is not to be explained by dilatation of the arterioles. This independent state of contractility of the capillaries is seen in the action of histamine, which dilates the capillaries and constricts the arterioles (Dale and Richards, 1918). This drug exerts such a powerful action on the vessels that the injection into an animal of an amount equal to one-millionth of its weight will cause a fall of blood-pressure to one-half and a condition indistinguishable from surgical shock (Dale and Laidlaw, 1919). The possibility of the production in minute quantities of similar substances during cellular activity must be kept in mind, though none have been isolated up to the present. Still, it must be pointed out that the vaso-dilation produced by the action of histamine in cats and dogs is replaced by vaso-constriction in the guinea-pig, so that it would be totally unjustifiable to assert that this substance plays the part of a general metabolite to bring about vascular dilation in active organs. It must also be mentioned that adrenalin in very small doses also possesses a dilator action on the capillaries (an effect which appears to be independent of the sympathetic), but the concurrent action on the arterioles is more pronounced than is the case with histamine (Dale and Richards, 1918).

A similar condition of affairs is seen in chilblains, when the capillaries are distended with blood of venous colour, owing to the impoverished oxygen supply resulting from the simultaneous arteriolar constriction.

Functional Activity.

A plethysmographic record of the tongue during the application of a single induction shock to the hypoglossal nerve (fig. 3) shows a simple compression of the collapsible vessels by the contracting muscles and a complete return to normal without any appreciable after effect of vaso-dilation.

When a tongue is made to develop tension against a muscle lever we note during the application of a series of successive induction shocks (fig. 9) a vaso-dilation which lasts for more than a minute after stimulation (see also Verzar 1912). One of the earlier (imperfect) plethysmographic records shows this hyperæmia very well (fig. 10), the vaso-dilation yielding a pulsatile tongue.

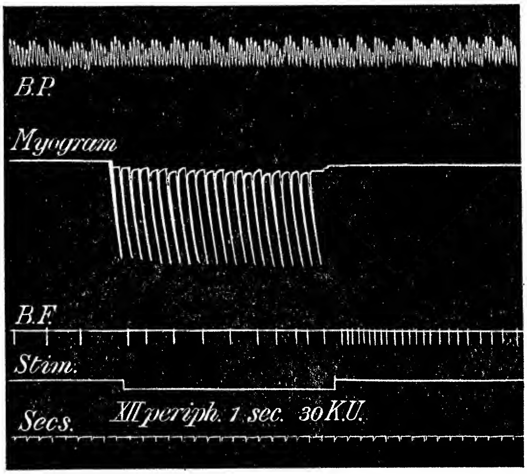

FIG. 9.

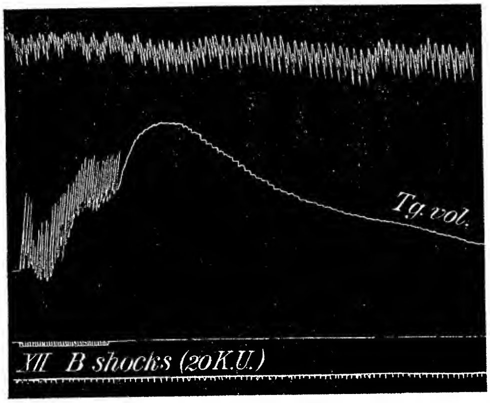

FIG. 10.

During faradisation of the motor nerve the blood flow is almost completely arrested by the compression of the contracting muscles (fig. 11). It is obvious that when a muscle is exerting its maximum effort and there is no alternation of contraction between groups of muscle-fibres, to sustain the effort for a considerable time involves the working of the muscle in the complete absence of fresh blood; in addition to the possible production of metabolites of activity we have here to consider the development of asphyxial products. This is a point of great importance in physical culture, *e.g.*, the maintenance of a continued position like "attention." The phenomenon is seen in its most exaggerated form in muscular "cramp."

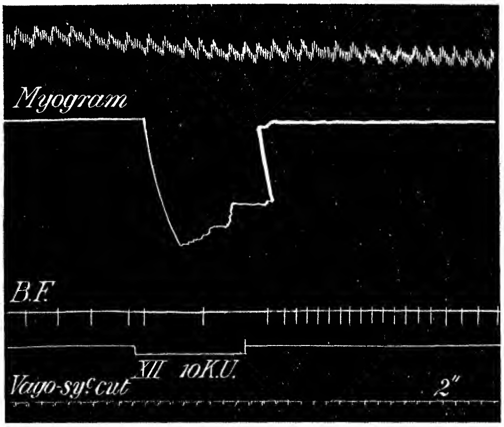

Fig. 11.

Ischæmia: The vaso-dilator effect of asphyxial products may be seen by placing artery forceps on the lingual arteries (fig. 12); on releasing the forceps the tongue dilates to an extent greater than in the resting condition and pulsation becomes more marked. This result confirms the findings of Anrep (1912) for the fore-limb.

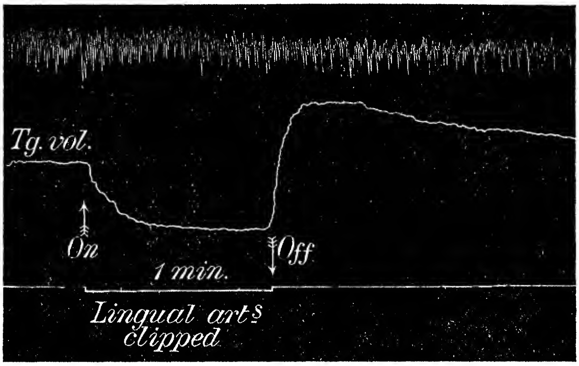

Fig. 12.

Venous Congestion: Compression of the lingual vein leads to venous engorgement of the tongue; on releasing the clip the venules quickly empty but the arterioles and capillaries, probably, remain dilated until the asphyxial products are removed (fig. 13). The long upward curve corresponds to the stage of "passive hyperæmia" while the swelling a few seconds after the release of the compression is a true active hyperæmia; the former is therapeutically regulated in Bier's treatment, though even here the long application of a tourniquet may also involve another doubtful factor—the swelling of the body colloids (M. Fischer, 1920).

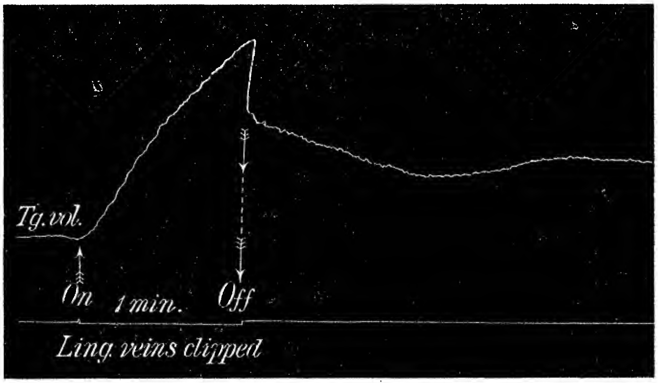

Fig. 13.

Both ischæmia and congestion produce like effects and the asphyxial products arising from them are additive (fig. 14). A corresponding additive effect is obtained with the metabolites of activity and asphyxial products (fig. 15), from which a similarity between these substances may be inferred.

Chemical Vaso-dilator Substances: Schwarz and Lemberger (1911) found that the injection of 1 c.c. of molar HCl into the central end of the left subclavian artery caused obvious dilatation of the blood vessels of the submaxillary gland. Comparing different acids, their action was not found to

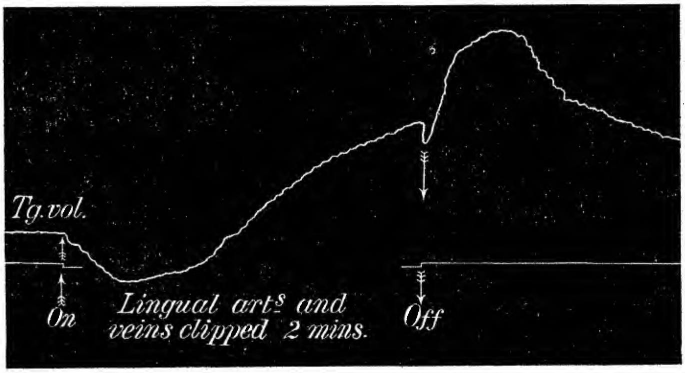

Fig. 14.

correspond to the H-ion concentration. The effect, as they point out, is really produced by CO_2 driven off from the bicarbonate of the blood. Acids weaker than CO_2 were inactive.

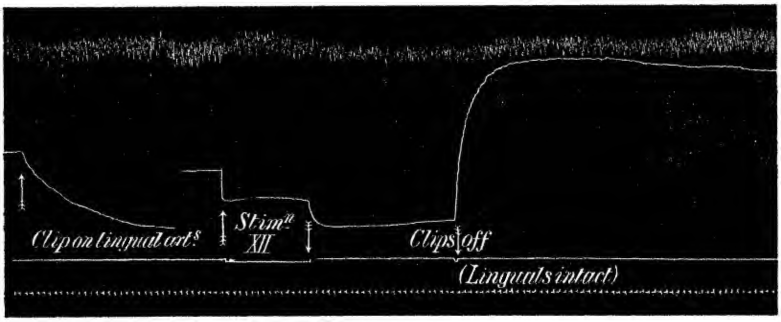

FIG. 15.

In order to put this to a more direct and measurable test, 1 c.c. of Ringer's fluid containing the substance was slowly introduced through a fine hypodermic needle immediately into the lingual artery without occluding it, thus minimising the capacity effect. Plain Ringer, sodium bicarbonate, and lactic acid were found to produce a vaso-dilation in the order named (so that the effect of Ringer alone must be discounted), but the effect produced by lactic acid was much the largest and most prolonged (fig. 16) and was in all respects

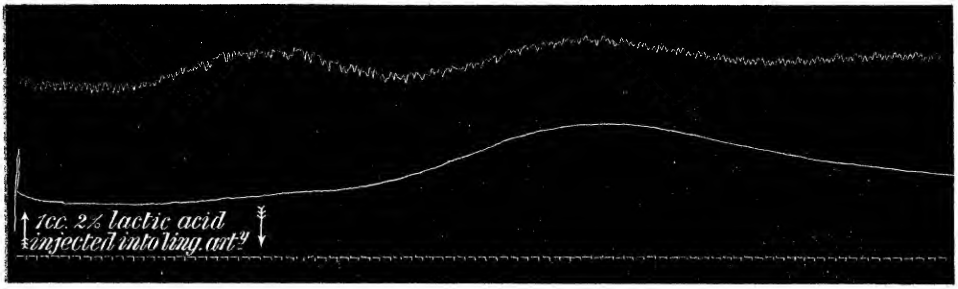

FIG. 16.

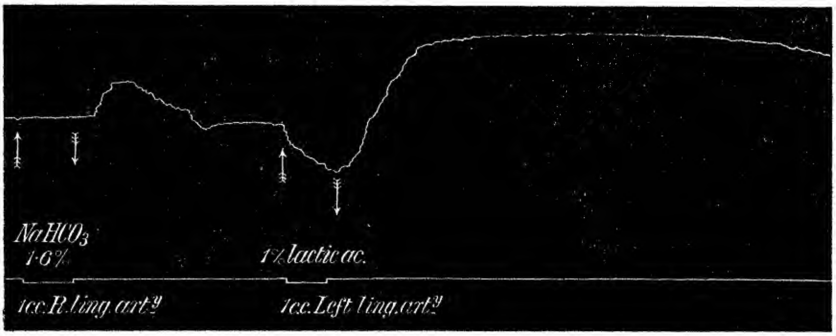

FIG. 17.

similar to the vaso-dilation produced by stimulation of the lingual nerve (compare figs. 17 and 6) and by the normal metabolites arising from muscular activity (compare figs. 17 and 4). Lactic acid, directly or indirectly, is therefore a true vaso-dilator substance.

6. FUNCTIONAL HYPERÆMIA.

We must now arrive at a decision regarding the mechanism by which the vaso-dilation accompanying muscular activity is brought about. Let us consider the first possibility, viz., that some form of reflex excites the vaso-dilator nerves into action at the same time as or soon after the stimulation of the motor nerve.

In glandular organs, the vaso-dilator fibres run in the same bundle as the secreto-motor fibres (*e.g.*, the chorda tympani to the submaxillary gland) and do not admit of direct analysis; the attempt to block one or other by means of drugs is not as convincing as simple section.

In our preparation, however, it is the vaso-constrictor fibres which run with the motor nerve while the fibres with a vaso-dilator action are bound up in the separate sensory nerve; we are thus enabled, by means of section, to interrupt any reflex arc (unless it be a peripheral axon reflex) through which vaso-dilation might be produced during motor activity.

An examination of the accompanying plethysmographic records (figs. 18 and 19) shows that as the initial mechanical stimulation of the lingual nerve (fig. 7) passes off, the vaso-dilation produced by faradisation of the hypoglossal nerve gradually becomes as great after as before section of the lingual nerve.

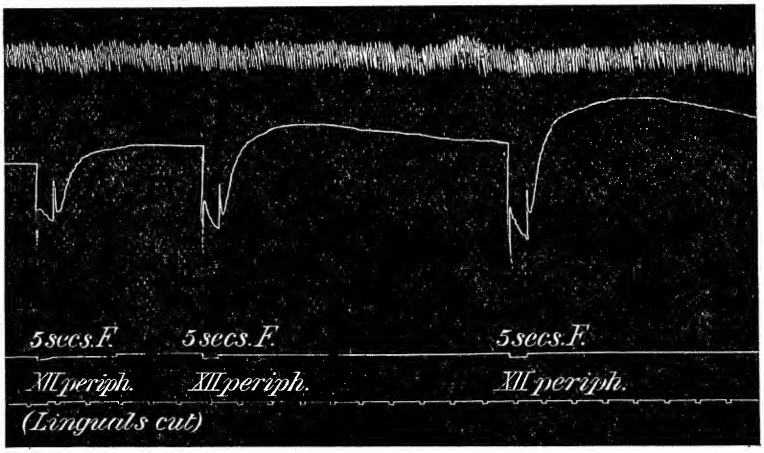

FIG. 18.

Division of the motor nerve makes no difference to the form of the curve, the same degree of dilation being produced by stimulating the uncut nerve as by stimulating the peripheral end of the divided hypo-glossal (figs. 19 and 20).

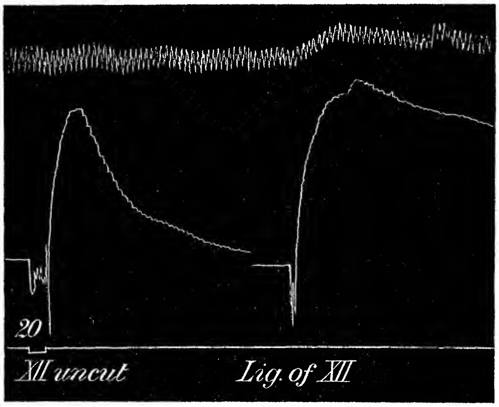

Fig. 19.

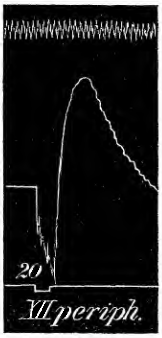

Fig. 20.

A large number of experiments was performed in the attempt to analyse the muscular contractions of the tongue during swallowing, elicited by stimulating the central end of the superior laryngeal nerve. The resulting vaso-dilation was inappreciable, since the long period of rest between successive swallowings (5 seconds or more), allowed of the complete removal of metabolites; and, on the other hand, section of both lingual nerves made no difference.

In the absence of any definite evidence for a reflex excitation of the lingual nerve, we must examine the metabolite hypothesis as a complete explanation for the hyperæmia of muscular activity. We have seen that lactic acid injected into the lingual artery can produce a typical vaso-dilation. Is lactic acid produced in appreciable amount during muscular activity? The answer is in the affirmative, if, in Ryffel's method (1909), it is really lactic acid which is being determined; estimations by this method gave the following results:—

	Lactic acid in mgrm. per 100 c.c. lingual blood during stimulation of	
	Lingual nerve.	Hypoglossal nerve.
Dog 11	6·0	40·8 25·6 (3 mins. later).
„ 12	6·4	53·6 48·0 (1 min. later).
„ 13	16·0*	64·0
„ 14	8·4	40·8
Mean	9·2	49·8

* After resuscitation from temporary asphyxia.

During stimulation of the lingual nerve there is the same concentration within the limits of experimental error, of lactic acid in the blood of the lingual vein as there is in the femoral arterial blood (*vide infra*). Thus one finds the lactic acid increased about five-fold in the venous blood of these experiments, in which the blood flow was maintained at twice its normal rate by interrupted faradisation of the motor nerve; if the normal rate of venous outflow had prevailed then the lactic acid concentration would have risen ten-fold; and in tetanus its concentration must be tremendously high.

The production of lactic acid would lead one to expect a reduction in the alkali-reserve according to the equation

$$H\cdot C_3H_5O_3 + NaHCO_3 = NaC_3H_5O_3 + H_2O + CO_2$$

but estimations show a simultaneous increase in the alkali-reserve :—

Alkali reserve of plasma.	Tongue.					
	Resting.		During stimulation of			
			Lingual nerve.		Hypoglossal nerve.	
	Venous.	Arterial.	Venous.	Arterial.	Venous.	Arterial.
Dog 15	55	55	54·5	55	59	54
„ 16	71	70	71	71	82	76
					83	74
„ 17	64	64	—	—	69	64
„ 18	52	50·5	—	—	64	54
„ 19	—	—	49·5	50	57	50
„ 20	61	59	60	59	73	59
„ 21	—	—	47	48	59	43
Mean $v-a$	1		—		9	

This absolute rise of nine in the alkali-reserve on a mean arterial alkali-reserve of 52·5 is equivalent to an average increase of 16 per cent. It is abundantly clear that both CO_2 and lactic acid are important metabolites of muscular activity. Fletcher (1907) found that an evolution of CO_2 follows a production of lactic acid in the frog's gastrocnemius.

The carriage of such large increases of acid by the blood became a problem of so much interest that the relative part played by plasma and corpuscles was investigated. The blood was collected under paraffin, NaF being used as an anti-coagulant, since it possesses the double advantage of not interfering with the estimation, and also preventing glycolysis (Clogne et Richaud), glycolysis having been shown to be associated with the formation of lactic acid in shed blood by Evans (personal communication). The results obtained are shown here :—

Lactic acid (mgrm. in 100 c.c. each of)	Stimulation of			
	Lingual nerve.		Hypoglossal nerve.	
	Plasma.	Corpuscles.	Plasma.	Corpuscles.
Dog 22	16·0	16·0	62·0	68·0
„ 23	12·5	12·9	18·4	16·0
„ 24	8·0	8·8	16·0	20·8
Mean	12·2	12·6	32·1	34·9

Taking into account the hæmatocrite values of these bloods, the lactic acid would appear to be evenly diffused through plasma and corpuscles.

The corpuscles from exercised muscles seemed to show an acidity of their contents markedly higher than the plasma in which they were laked even when NaF was used as the anti-coagulant (*vide infra*). Two dialysing sacs were prepared (Dale and Evans, 1920) and half filled with saline and water respectively (both of known P_H and corrected for) and a comparison made of the P_H ; such results as the following were obtained :—

	Dog 25.	Dog 26
Corpuscles intact (in saline)	7·35	7·40
Ruptured corpuscles (in distilled water)	7·20	7·25

It must be mentioned, however, that laked corpuscles (frozen and thawed) always exhibit a slightly lower P_H than intact corpuscles.

An increase of lactic acid in the blood is thus seen to be not incompatible with a rise of alkali reserve in the plasma, in view of the share played by the corpuscles in bearing the onslaught of the acid attack. It must further be admitted that the red corpuscle is permeable to the lactic acid ion, and the following is advanced as a possible explanation of the events :—

1°. Diffusion of the lactic acid from the working muscle into the alkaline tissue fluid

$$\text{Lactic acid} + NaHCO_3 \longrightarrow \text{Sod. lactate} + H_2CO_3.$$

The carbonic acid given off diffuses through the vessel wall where it exerts its vaso-dilator effect (*vide* figs. 4 and 17 ; note in the latter the direct astringent effect and the indirect effect of lactic acid due to CO_2).

2°. Diminution of the plasma chlorides and increase of the alkali reserve (L. J. Henderson, 1909)

$$\underset{\text{from } 1^\circ}{H_2CO_3} + \underset{\text{of plasma}}{NaCl} \rightleftarrows \underset{\text{alkali reserve.}}{NaHCO_3} + HCl.$$

3°. Some free lactic acid is formed from part of the sodium lactate in (1) and part of the HCl in 2°

$$\text{Sod. lactate} + HCl \longrightarrow \text{Lactic acid} + NaCl.$$

This lactic acid penetrates the corpuscles just as the HCl from 2° does (Hamburger, 1904) and the H_2CO_3 from 1° (Buckmaster, 1918).

4°. The oxidative removal of lactic acid continues for some minutes (Fletcher and Hopkins) and coincides with the recovery heat production (Hill) and the increased oxygen intake (Verzàr) following muscular activity.

It is believed by many, though on insufficient data, that lactic acid and CO_2 act by increasing the H-ion concentration. Calculation of the P_H of the blood from measurements of the alveolar CO_2 may show a difference of 0·02 during muscular exercise (Campbell, Douglas, Hobson, 1914); a rise of acidity has been inferred from estimations of the affinity of the blood for oxygen (Mathison); more recently Barcroft and Parsons (1920) have found that muscular work causes a fall in P_H of 0·08 in the blood when defibrinated and completely reduced.

The erythema arising in electro-therapeutics in the area of the kathode suggests the possibility of a direct action by the H-ions (or Na-ions?). In normal activity, such a direct action of lactic acid is impossible in the presence of the bicarbonate of the tissue fluids; the increase of alkali reserve seen to occur above must also tend to keep down the H-ion concentration of the *plasma*, hence the ultimate depressant of the blood-vessel wall must be the CO_2. Patterson and Starling (1914), working on the isolated heart-lung preparation, have shown that the heart relaxes more and more as CO_2 is added to the air ventilating the lungs. Evidence is accumulating that CO_2 possesses specific properties in its action upon the tissues which are not possessed by other acids (Schwarz and Lemberger, 1914, C. Lovatt-Evans); fig. 17 is interesting in this connection.

Finally, we have shown in § 5 that CO_2 and lactic acid, when injected into the blood stream, act as powerful vaso-dilator substances, and again in § 6 that these acid metabolites are formed in increased amount during muscular activity. In so far as functional hyperæmia is adequately explained by the vaso-dilator action of metabolites, we are in full agreement with Barcroft (1914); but in § 4 we have shown the separate existence of vaso-dilator nerves which were not, at least in the above experiments, called into play during muscular activity. We must consequently expect to find other functions for the vaso-dilator nerves.

7. Control of Body Temperature.

The fortunate employment of the dog gave the clue to a possible function of the vaso-dilator fibres in the lingual nerve. It is a common fact that dogs resort to panting and extrusion of the tongue for cooling of the blood. The effect upon the blood-flow in the tongue resulting from the stimulation of the heat receptors in the skin was therefore studied.

The fur was cut off, a radiant-heat hemi-cylinder was placed over the trunk of the animal, the venous outflow from the lingual vein recorded, and the rectal temperature observed throughout the experiment.

The warming of the skin caused hyperæmia and increased lingual blood-flow long before the body temperature was appreciably raised (fig. 21, i and ii). In all cases where this response did not occur the body temperature steadily advanced; Stewart (1913) also emphasises the importance of reduced blood-flow in fever.

To test whether this was an effect of heated blood directly upon the vessels or a reflex mechanism, the lingual nerves were cut on both sides and time given for the effect of this stimulus (fig. 7) to pass off. The application of radiant heat to the skin of the trunk was now not followed by lingual hyperæmia (fig. 21, iii and iv).

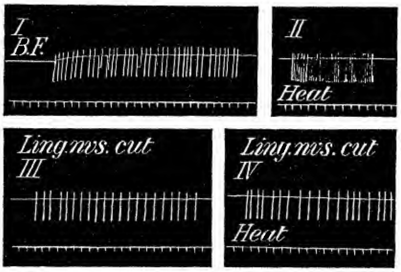

Fig. 21.

The same results were obtained in another dog, which was immersed in a warm bath. It is thus apparent that a nervous reflex of this nature brings about a quicker response than could be obtained by the heating up of the whole blood; and, further, the nervous reflex ensures vaso-dilation of that particular organ which is most favourably disposed for the cooling of the blood, whereas heated blood would have a generalised effect on external and internal organs alike. It is possible that the flushing of the face in man in emotional states and in fever may also be accounted for by similar reflexes involving vaso-dilator nerves. Measurements of the blood-flow, by Stewart's method, in the hands and feet during fever show that the cutaneous vessels dilate during fall of temperature by *crisis*.

Whether the vaso-dilation of the tongue plays any part in the sensation of taste was not investigated.

CONCLUSIONS.

1. The lingual nerve contains true vaso-dilator fibres, just as the sympathetic contains vaso-constrictor fibres; both are equally independent of the intervention of metabolites.
2. No evidence was found that functional hyperæmia is due either to diminution in vaso-constrictor tone or to increase in vaso-dilator tone.
3. The experiments show that the increased blood-supply during muscular activity is due entirely to the products of metabolism; the absence of a simultaneous excitation of the vaso-dilator nerves during voluntary movement, though probable, is not proved.
4. Of the metabolites estimated, CO_2 and α-OH organic acids were found to be increased.
5. Apart from muscular activity, one function of vaso-dilator nerves was found to be concerned with the control of body temperature; active hyperæmia in the dog's tongue may be induced by reflex excitation of the vaso-dilator nerves through stimulation of heat receptors in the skin.*

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